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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,647	07/17/2001	Ramachandran Murali	UPN-3963	3796

7278 7590 08/14/2003

DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257

EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	//

DATE MAILED: 08/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,647	MURALI ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *2-5 and 9-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicants' arguments in Paper No. 10, filed June 12, 2003, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The addition of new claims 6-24 has been acknowledged.

3. Newly submitted claims 9-24 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: It is noted that the elected subjected matter of group I is drawn to a method wherein the limitations for target protein and modifier are unspecified. New claims 9-24 are directed to distinct species of targets proteins or modifiers, which are not of the elected subject matter by original presentation for prosecution on the merits.

4. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 9-24 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 1 and 6-8 are examined on the merits.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 1 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that modulates intermolecular interactions between a target protein, TNF, CD4 receptor, and β-lactamase, and a modifier, does not reasonably provide enablement for a method of identifying a compound that modulates intermolecular interactions between any target protein and a modifier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

8. It is noted that the Examiner had inadvertently omitted the CD4 receptor and β-lactamase as a target proteins that are enabled by the instant specification in Paper 9, mailed March 11, 2003. The CD4 and β-lactamase target proteins have been added to the target proteins that are enabled by the instant specification.

9. This rejection is maintained with respect to claim 1, as recited in the previous office action Paper No. 9, mailed March 11, 2003. Further, this rejection is extended to new claims 6-8 of this instant application.

10. It is re-iterated the factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

11. Applicants argue the identification of the functional sites and allosteric cavities can be achieve using crystal structure or NMR...or by computer modeling (page 10-11). These techniques are well known in the art as demonstrated by Li et al. Further, protein structure can be predicted from the primary amino acid sequences using computer-based *de novo* or *ab initio* methods. Applicants' argument and cited support have been acknowledged and found to be unpersuasive.

12. It is acknowledged that applicants cite crystal structure or NMR...or by computer modeling (page 10-11) for identifying functionally critical sites on a target protein. However, the specification and working examples (1-3) are solely based on data that have been derived from an unpredictable process, protein crystallization. In the case of TNF and CD4 receptor, the working Examples (1-3) rely solely X-ray diffraction data. In Example 4, Applicants disclose β-lactamase have been identified by thermal β-factors analysis (Example 4). β-factors are parameters that define parameters that reflect the disordered (flexible) nature of atoms in the 3D structure determined by X-ray diffraction (page 10, lines 11-25). Applicants have not provided one of ordinary skill in the art any guidance to practice the instant invention with any technique that does not required X-ray diffraction data. The citation of other techniques that could be used for practicing the instant invention without providing adequate guidance for using the said techniques falls short of enabling the claim

invention. It is, therefore, unreasonable to expect one of skill in the art to use the information derived from an unpredictable process to reliably use the claimed invention to identify compound that modulates intermolecular interactions between any target protein and a modifier without undue experimentation. Further, without specific guidance and working examples for using the instant invention with other methods or techniques cited in Applicants' arguments, it is unreasonable to expect one skilled in the art to use the limited information provided by the specification to practice the invention without undue experimentation.

13. Specific to Applicants' argument and cited references directed to the unpredictability of the art of protein crystallization, the said arguments have been fully consider and found to be unpersuasive.

14. It is re-iterated that it is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a *New Focus* article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essence, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (Science, 2002). It is, therefore, unreasonable to expect one skilled in the art to use the information derived from an unpredictable process to reliably use the claimed invention to identify a compound

that modulates intermolecular interactions between any target protein and a modifier without undue experimentation.

NEW CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling inhibitors of TNF receptor, CD4 receptor, and β-lactam, does not reasonably provide enablement for enhancers of TNF receptor, CD4 receptor, and β-lactam or any other receptors or substrates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

17. This rejection is necessitated by Applicants amendments.

18. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic

engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

19. It is acknowledged that Applicants discloses the instant invention may be used to identify modulators, such as inhibitors or enhancers (page 9, line 20). Further, Applicants provides examples (pages 15-39) for identifying inhibitors of TNF receptor, CD4 receptor, and β-lactam. However, Applicants do not provide guidance or working examples for identifying enhancers.

20. Without specific guidance and working examples for using the instant invention to identify enhancers, it is unreasonable to expect one skilled in the art to use the limited information provided by the specification to practice the invention to identify enhancers of TNF receptor, CD4 receptor, β-lactam, or any other receptors or substrates without undue experimentation.

CLAIM REJECTIONS - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1, 6, and 7 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Li et al. (1997).

23. This rejection is maintained with respect to claim 1, as recited in the previous office action Paper No. 9, mailed March 11, 2003. Further, this rejection is extended to claims 6 and 7 of this instant application.

24. Applicants argue that Li et al. dose not disclose the method of identifying compounds that bind to surface cavities that are proximal to the functionally site. Further, Applicants disclose the definition of the term "proximal" on page 9, lines 1-11. Applicants' argument and disclosure have been acknowledged and found to be unpersuasive as discussed below.

25. It is re-iterated that Li et al. discloses a method for identifying a compound that inhibits the interaction between CD4 and major histocompatibility complex (MHC) class II proteins) (Abstract). Specifically, a computer screen was performed to determine the human CD4 D1 domain containing a surface-binding pocket for ligand binding, as in step a) of claim 1 of this instant application. "The binding of an organic ligand to the CD4 surface was judged both by shape complementary and by a simplified interaction energy (force field energy)", as in step b) of claim 1 of this instant application. Li et al. screened 1000 molecules and molecules with the best shape complementary scores and best force scores were selected, as in instant claim 1, step c) and claim 6. The inhibition of stable CD4-MHC class II binding by the compounds were tested using standard cell adhesion assay to accurately assess the functional interaction (Page 74, Column 1, lines 5-43), as in instant claim 1, step d) and claim 7.

26. The inclusion of documents from Coffin et al. and Pieatier-Tonneau et al. are not used as prior art but only to expand on the inherent characteristics of the CD4 marker in response to Applicants' argument. Coffin et al. discloses CD4 has multiple domains (Figure 5). Pieatier-Tonneau et al. discloses the regulation of CD4 to ligands interaction is dependent proximal location from the said interaction to other functionally critical domains of CD4 (page 126, column 1, lines 1-6). Further, Pieatier-Tonneau et al. discloses CD4 mediated interaction are

allosteric in nature (page 127, column 1, lines 25-32). It is noted that claim 1 recites the limitation "identification of a cavity proximal to a functionally critical site", however, Applicants do not define the specific cavity or the functionally critical site. Consistent with the scope of claim 1, Li et al. discloses a method for identifying a compound that modulates the interaction of CD4 by determining the CD4 D1 ligand surface-binding pocket, which is proximal to the other functionally critical domains of CD4.

CONCLUSION

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

28. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

29. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61

(November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

31. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

32. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
8/7/03

Ardin H. Marschel
ARDIN H. MARSCHEL
PRIMARY EXAMINER